Amendments to the Drawings:

Please replace original Figures 6 with replacement Figures 6, included herewith, which include the amendments explained in the remarks section of this amendment.

Attachment: Replacement sheet
Annotated Sheet Showing Changes

REMARKS

Claim 1-6, 8-15, 17- 24, 26 and 27 are currently pending and stand rejected. Claims 7, 16 and 25 have been canceled with this action. Claims 1, 6, 8, 9, 10, 15, 19, 24 and 26 have been amended with this action. These amendments add no new matter. The above amendments have been made in the interest of expediting prosecution and not for reasons of patentability. Applicants reserve the right to pursue unclaimed subject matter at a later date. Support for these amendments can be found throughout the application as filed. Applicants note that the Examiner has acknowledged Applicant's amendment to the specification to correct references to oligonucleotide 1 and to comply with the sequence listing rules. Applicants gratefully acknowledge the Examiner's reconsideration and withdrawal of the previous rejection of claims 1, 10 and 19 under 35 U.S.C. §112, second paragraph, as well as the previous rejection of claims 10-18 and 19-27 under 35 U.S.C. §112, first paragraph. Applicants further gratefully acknowledge the Examiner's finding that the previous rejection of claims 1, 10 and 19 under 35 U.S.C. §102(b) has been reconsidered and withdrawn.

Claim Objections

The Office Action states that claim 9 is objected to because it contains a grammatical error. Accordingly, Applicants have amended the claim to replace "I" with "is" as requested by the Examiner. This amendment introduces no new matter and is merely a correction of a typographical error.

Specification Objections

The Office Action states that the specification is objected to "because the legend of Figure 6 is unclear." In particular, the Office Action states that "lines representing "no treatment" and "CPT-11-25 mg," and lines representing "PBS" and "AS-1-10 mg" cannot be

distinguished." While it is the Applicant's belief that the stated graphical representations are clear, Applicants have amended Figure 6 so as to indicate, in addition to the line coding used, which dose/response line corresponds to which of each of the stated objected treatment regimens in the figure's legend.

Oath/Declaration

The Office Action states that the oath or declaration requires correction because "non-initialed and/or non-dated alterations have been made to the oath or declaration." Accordingly, a newly executed oath or declaration is included with this Response.

Priority

The Office Action states that Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. §119(e) because a specific reference to the prior application(s) must appear in the first sentence of the specification or in an application data sheet. Accordingly, Applicants have amended the specification above to include a specific reference to the prior application to which the benefit of priority is claimed.

Rejection under 35 U.S.C. §112, 2nd paragraph

The Office Action states that claims 19-27 have been rejected under 35 U.S.C. §112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Office Action states that "the limitation "wherein the prodrug is present in an amount that would not be therapeutically effective in the absence of the polyanion" in claim 19 is unclear." Applicants respectfully traverse this rejection for the reasons that follow.

Applicants note that the stated claim language is clear to the skilled artisan in light of the specification. In particular, the specification teaches, in Examples 1 and 2, pages 12-15, that statistically significant synergistic therapeutic effects on tumor inhibition and survival time were observed when Camptosar was administered in combination with oligonucleotides when compared with administration of Camptosar alone at a stated dose (*e.g.*, at 25 mg/kg Camptosar). Accordingly, the skilled artisan, reading the claim in light of the specification, would appreciate that the stated dose of 25 mg/kg Camptosar is an exemplary dose of prodrug "that would not be therapeutically effective in the absence of the polyanion."

Furthermore, the skilled artisan would be able to determine, *e.g.*, for other animals to be treated or for other prodrugs to be used, a prodrug dose that is "not therapeutically effective in the absence of the polyanion" through routine testing. In particular, a lack of therapeutic effectiveness in this instance would be recognized to be a dose of prodrug which, when compared to a mock treatment negative control (*e.g.,* no treatment or saline injection), does not produce a statistically significant therapeutic effect. Statistical significance in Examples 1 and 2 included a range of p values from $p<0.08$ to $p<0.0001$. Accordingly, the skilled artisan, reading the claim in light of the specification, would recognize the expression "wherein the prodrug is present in an amount that would not be therapeutically effective in the absence of the polyanion," to mean an amount of prodrug which, when compared to a mock treatment negative control, does not produce a statistically significant therapeutic effect corresponding to a p value in the range of $p<0.08$ to $p<0.0001$ or less.

In view of these teachings in the specification in combination with the common knowledge and understanding of the person of ordinary skill in the art, Applicants assert that the stated claim language is not indefinite and, accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112, 1st paragraph (written description)

The Office Action states, for separately stated reasons, that claims 1, 6-9, 10, 15-18, 19, and 24-27 have been rejected under 35 U.S.C. §112, first paragraph as "containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor(s), at the time the application was filed, had possession of the claimed invention" (*i.e.,* for alleged failure to satisfy the written description requirement). The Office Action states that "the specification fails to describe the complete structure of a representative number of species of the claimed genus." In particular, the Office Action states that "[A]pplicants specification does not provide a sufficient number of representative species of any polyanion (oligonucleotide) that statistically significantly potentiate the activity of any prodrug." Applicants respectfully disagree with this rejection for the reasons that follow.

First, the Examiner cites Fiddes v. Baird (30 U.S.P.Q.2d 1481) for the proposition that "claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class...(because)...the specification provided only the bovine sequence." Applicants respectfully note that, unlike the facts in Fiddes v. Baird, in which claims directed to mammalian FGF's were at issue, the instant claims are directed to the use of oligonucleotides (*i.e.*, polyanions) independent of their sequence. In Fiddes, the claims at issue were drawn to a "DNA molecule.....encoding mammalian basic fibroblast growth factor." In contrast the instant claims are drawn to the use of a "a polyanion with...(a)...prodrug, wherein the polyanion is not an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and wherein the oligonucleotide does not have the sequence of SEQ ID NO: 1." While it is clear that only a select set of species of nucleic acids would be capable of encoding mammalian FGF proteins (the issue in Fiddes), no such sequence specificity is at issue in the instant claimed invention. Indeed the only sequence requirement, as specified by claim 1, is that the oligonucleotide not have the sequence of SEQ ID NO: 1. Accordingly, the only sequence limitation is a negative limitation that is supported in the application as filed.

Indeed Example 2 (see pages 14-15) of the instant application demonstrates that "oligonucleotides produce a statistically significant potentiating effect on Camptosar that is independent of the sequence of the oligonucleotide" (emphasis added). Accordingly, representative species (*i.e.* of specific oligonucleotide sequences) are not needed to support written description because the use of all possible sequences, exclusive of the specified SEQ ID NO: 1, is supported in the instant application and all possible sequences are readily apparent to anyone with knowledge of molecular biology. No further written description support for the oligonucleotides of the invention would be required by the artisan of ordinary skill to recognize the inventor's possession of the claimed invention.

Notwithstanding the foregoing arguments, Applicants, in order to expedite prosecution and not for reasons of patentability, have amended independent claims 1, 6, 10 and 19 to specify "an oligonucleotide" rather than "a polyanion." Applicants respectfully assert that the application fully supports the written description requirement of the claimed invention, as amended. Accordingly, reconsideration and withdrawal of the rejection of claims 1, 6-9, 10, 15-18, 19 and 24-27 under 35 U.S.C. §112, first paragraph (written description) is respectfully requested.

Rejection under 35 U.S.C. §112, 1st paragraph (enablement)

The Office Action states, for separately stated reasons, that claims 1-9, 10-18, and 19-27 have been rejected under 35 U.S.C. §112, first paragraph because "the specification....does not reasonably provide enablement for a method for potentiating the activity of a prodrug comprising co-administering a polyanion (oligonucleotide) with the prodrug," (*i.e.*, for alleged failure to satisfy the enablement requirement). Applicants respectfully disagree with this rejection for the reasons which follow.

First, in support of the enablement rejection, the Office Action states that the "instant specification does not describe how to make and/or use that polyanion (oligonucleotide) which is

not an oligonucleotide having two 5' and four 3' 2-O-methylribonucleosides and wherein the oligonucleotide does not have the sequence of SEQ ID NO: 1" (citing the §112, first paragraph rejection for written description addressed above). However, as with written description, further explicit disclosure of methods of making specific oligonucleotides not having the sequence corresponding to SEQ ID NO: 1 for use in the claimed invention, beyond the teachings of the instant application, are not needed to support enablement, because such oligonucleotides not having the sequence corresponding to SEQ ID NO: 1 are well known in the art and would accordingly not require undue experimentation to make and use.

Further, the Office Action supports the enablement rejection of claims 1-9 and 10-18 by citing Ex parte Singh (17 U.S.P.Q.2d 1714 (BPAI 1991) for the proposition that "the breadth of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims." Notably, the Ex parte Singh decision by the Board of Patent Appeals and Interferences in turn cites In re Marzocchi (439 F.2d 220; 169 U.S.P.Q. 367 (C.C.P.A. 1971)) in support of this proposition.

However, In re Marzocchi is a case in which the Court of Customs and Patent Appeals reversed a rejection under 35 U.S.C. §112 (enablement) of a claim in the chemical arts, stating that, while "there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statements put forward as enabling support for a claim.....especially...wherein the statement is, on its face, contrary to generally accepted scientific principles.....*it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement.*" In re Marzocchi (439 F.2d 223-224; 169 U.S.P.Q. 369) (emphasis added). Furthermore, the courts have been careful to point out that evidence of unpredictability (rather than the intrinsic nature of the art itself) is what gives rise to an enablement concern (see In re Cook, 439 F.2d 730; 169 U.S.P.Q. 298 (C.C.P.A. 1971)). Here, Applicants respectfully assert that no specific and objective support for rejection of the pending claims for lack of enablement has been made.

Notwithstanding the foregoing arguments, Applicants, in order to expedite prosecution and not for reasons of patentability, have amended independent claims 1, 6, 10 and 19 to specify "an oligonucleotide" rather than "a polyanion." Applicants respectfully assert that the application fully supports the enablement requirement of the claimed invention, as amended. Accordingly, in view of the state of the art of oligonucleotide production, the broad teachings of the specification, the lack of any specific and objective reasons for believing that the teachings of the specification are "contrary to generally accepted scientific principles," or otherwise in doubt, and further in view of the above amendment, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-6, 8-15, 17-24, and 26-27 under 35 U.S.C. §112, first paragraph (written description) is respectfully requested.

Rejection under 35 U.S.C. §102

The Office Action states that claims 10, and 14-18 have been rejected under 35 U.S.C. §102 (b) as anticipated by Chen et al. [U.S. Patent No. 6,013,786]. In particular, the Office Action states that "Chen et al. teach JAR cells treated with prodrug campothecin (CPT) and a phorsphorthioate oligonucleotide targeting mdm2" (citing Figure 7A-7C). Applicants respectfully traverse this rejection for the reasons which follow.

First, Applicants respectfully note that the cited publication, U.S. Patent No. 6,013,786 (the '786 patent) issued on January 11, 2000, while the instant application was filed on November 8, 2000, and, further, claims priority to provisional application 60/164182, filed on November 9, 1999. Accordingly, the '786 patent does not anticipate the instant claimed invention under 35 U.S.C. §102(b) because it is not "patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States."

Second, presuming that the '786 patent were applied under 35 U.S.C. §102(e) as "a patent granted on an application for patent by another filed in the United States before the invention by the applicants for patent," the cited reference still fails to anticipate the claimed invention because the subject matter claimed in the instant application is not taught by this

reference. In particular, the invention claimed in claim 10, and dependent claims 14-18, is directed to methods of using prodrugs (such as Camptosar), while the '786 patent, in the cited section (*i.e.*, Figures 7A-7C), does not describe the use of prodrugs, but rather describes the use of camptothecin. The instant application defines a "prodrug" as a "compound comprising an active compound covalently linked to another moiety by a cleavable linkage, wherein the pharmacological activity of the active compound is greater than the pharmacological activity of the prodrug, and wherein the active compound is produced in the body by cleavage of the cleavable linkage" (see application starting at page 5, line 18). By this definition, and consistent with popular usage, Camptosar is a prodrug while camptothecin is not.

As indicated in the attached reference (Pizzolato and Saltz (2003) The Lancet 361: 2235-42), camptothecin and Camptosar have different chemical structures (see first figure of Pizzolato and Saltz). Camptosar (also known a Irinotecan (7-ethyl-10-[4-(1-piperidino)-1-piperidino] carbonyloxycamptothecin) is a water-soluble semisynthetic derivative of camptothecin which carries a dipiperidino side-chain linked to the camptothecin molecule via a carboxyl-ester bond (see Pizzolato and Saltz, beginning at page 2237, column 2). This bulk dipiperidino side-chain promotes solubility but leads to a substantial reduction in anticancer activity so that cleavage of the side-chain by carboxylestereases, found, *e.g.*, in the liver and gastrointestinal tract, is needed for anti-cancer activity. The relatively inactive Camptosar is thus converted to an active form metabolite known as SN-38 (7-ethyl-10-hydroxycamptothecin) by cleavage of an ester linkage by an enzymatic activity in the body. In contrast, camptothecin, requires no such chemical cleavage for its activation, and thus is not a prodrug. Applicants respectfully note that CPT-11 is a synonym for the prodrug Camptosar, and is not a synonym for camptothecin (which is referred to as simply "CPT" in the art and in the '786 patent). Therefore, Camptosar (CPT-11) is a prodrug, while camptothecin (CPT) is not.

It thus follows that the '786 patent does not teach methods using a prodrug and therefore does not anticipate the instant claimed invention. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §103

The Office Action states that the rejection raised in the previous Office Action, of claims 1-27 under 35 U.S.C. § 103(a) in view of Tortora *et al.*, Wang *et al.*, Chen *et al.* (the '786 patent) and further in view of Baracchini *et al.*, has been maintained. Applicants respectfully traverse this rejection for the following reason.

Applicants note that, for the same reason provided above distinguishing the teachings of the '786 patent from the instant claimed invention, the cited references fail to render obvious the claimed invention because they fail to teach or suggest the use of a prodrug. In particular, the Office Action states that Applicant's arguments have not been found persuasive because "Chen *et al.* teach potentiation of the activity of the prodrug CPT-11 by co-administering a phosphorothioate oligonucleotide targeting mdm2 resulted in a 17-fold activation of the p53 reporter" (citing Figures 7A-7C).

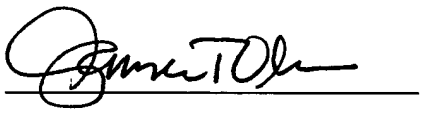
Applicants again respectfully note that the '786 patent teaches uses of camptothecin (*i.e.* "CPT," not "CPT-11") at Figures 7A-7C, and that, as explained above, camptothecin is not a prodrug. This same point of distinction applies to the remaining references as well. Therefore, the Office Action fails to provide a *prima facie* case for obviousness of the claimed invention because it does not provide a reference utilizing a prodrug or otherwise teach modification of the teachings of the cited references to the use of prodrugs. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If a telephone interview would advance prosecution of the application, the Examiner is invited to call the undersigned at the number listed below.

A Petition for a Two (2) Month Extension of Time, and authorization of payment of the corresponding fee accompanies this Response. Please charge any additional fees or refund any overpayment to Deposit Account No. 08-0219.

Respectfully submitted,



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